Published in final edited form as:

Org Lett. 2012 March 16; 14(6): 1600–1603. doi:10.1021/ol300303s.

Synthesis of Fused Indazole Ring Systems and Application to Nigeglanine Hydrobromide

Aaron C. Sather, Orion B. Berryman, and Julius Rebek Jr.*

The Scripps Research Institute Mail MB-26, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Abstract

nigeglanine hydrobromide (**1**)
>1.6 g prepared

The single-step synthesis of fused tricyclic pyridazino[1,2-*a*] indazolium ring systems is described. Structural details revealed by crystallography explain the unexpected reactivity. The method is applied to the gram scale synthesis of nigeglanine hydrobromide.

Indazole derivatives are a versatile class of compounds that have found use in biology, catalysis and medicinal chemistry.¹ Although rare in nature,² indazoles exhibit a variety of biological activities such as HIV protease inhibition,³ antiarrhythmic and analgesic activities,⁴ anti-tumor activity,⁵ and anti-hypertensive properties.⁶ Indazolium ions have found additional uses as precursors to N-heterocyclic carbenes (NHCs) with organo-catalytic activity⁷ and they are strong donor ligands for transition metal complexes.⁸ While a variety of capable synthetic methods exist for indazole synthesis,⁹ we report a new precursor for indazole formation – 2-formyl dialkylanilines. With hydroxylamine, this precursor allows for easy entry to the fused tricyclic pyridazino[1,2-*a*]indazolium ring system seen in the indazole natural products. This reaction involves an exchange of the N–O bond of the oxime for the N–N bond of the heterocycle and was applied to the gram scale synthesis of nigeglanine hydrobromide (**1**).

During our investigation of *ortho*-hydroxyaryloxime antidotes for organophosphorous nerve agent sensing we found that treatment of aldehyde **2** with hydroxylamine hydrochloride in ethanol at 65 °C gave the expected oxime (**3**) only as the *minor* product (1:4, Figure 1). The

*jrebek@scripps.edu .

Supporting Information Available: General information and full experimental details for all compounds discussed. Cif files for all crystal structures along with tables of relevant structure data are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

major product was identified by single crystal X-ray diffraction as the substituted *N*-methyl indazole **4** (Figure 1, bottom right).

The oxime product (**3**) can be obtained in better yield at room temperature, and its crystal structure (Figure 1, bottom left) reveals the reason for the unexpected formation of **4**. The dimethylamino group is twisted out of the aromatic ring plane to avoid steric clashes with the adjacent bulky bromine atom. Although phenols react with activated oximes to form isoxazoles,¹⁰ the nitrogen of the twisted aniline is more basic and its lone pair electrons are predisposed to attack the oxime. This reaction results in N–N bond formation as water is lost. Demethylation, presumably by the halide, completes the sequence.

In general indazoles, or heterocycles, are synthesized by N–C bond forming reactions but examples of indazoles formed from creating N–N bonds have also been reported. Electrophilic amination of this type has been exploited previously by Hassner¹¹ and more recently by Stambuli.^{9c,d} In both examples an activating agent — DCC in the former and MsCl in the later — was used to promote attack of the oxime nitrogen to form the N–N bond. In our approach, no such activating agent is required.

We used 2-pyrrolidinyl benzaldehyde (**5**) to determine the nature of the nucleophile involved in the dealkylation step. Increased temperatures were required for the reaction to proceed, and after four hours at 150 °C the three expected products were obtained: the oxime (**6**), the *N*-alkyl indazole product (**8**), and the tricyclic indazolium (**9**). NMR and MS analysis (see SI) confirms that chloride dealkylates the quaternary nitrogen of the former pyrrolidine, giving rise to **8**. The proposed mechanism for this transformation is shown in Scheme 1. In specific cases, spirocyclic quaternary nitrogen atoms of the type shown in the scheme (**7**) have been isolated as betaines (1,1-disubstituted indazol-3-ylidene oxides) and are known to dealkylate in a similar manner.¹² By extending the reaction time it is possible to obtain the tricyclic indazolium product exclusively and in high yield.

We optimized reaction conditions (1.2 equiv. $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 150 °C, 18 h, sealed tube) and explored the scope of this cyclization cascade with a series of substituted 2-pyrrolidinyl benzaldehydes. These were obtained from commercially available 2-fluorobenzaldehydes and pyrrolidine (See SI). As shown in Scheme 2, both electron donating and withdrawing groups are tolerated. The strongly donating pyrrolidinyl group (**16**) gave the highest yield. Halogens Br (**11**), Cl (**14**), and F (**10**) were also well tolerated. The use of methoxy derivatives in place of the free phenols is recommended due to decomposition of the latter during the cyclization reaction. Mild electron withdrawing groups such as trifluoromethyl (**18**) and carboxylate (**17**) also form products but in lower yields. Substitution with a nitro group (**19**) on the otherhand gives a different product: dehydration of the oxime is favored, and the nitrile **19** is formed (see SI for X-ray structure of **19**).

Besides altering the substituents on the aromatic ring, we varied the aniline ring size to further test the scope of the reaction (See SI, Table S-1). Increasing the ring size of the aniline from five (pyrrolidine) to six (piperidine) gave the chloroalkyl indazole in moderate yield, showing that formation of the seven membered ring is unfavored even at high temperatures. We were unable to synthesize aniline starting materials with smaller ring sizes, having observed rapid decomposition in the $\text{S}_{\text{N}}\text{Ar}$ reaction with azetidine and aziridine, which prevented these anilines from being investigated. We also explored the synthesis of C_3 substituted indazole products from acetophenone or benzophenone substrates. These substrates provided the *N*-alkylchloride indazole along with the usual ketoxime. Ring-closure to the tricyclic indazolium products was observed only in trace amounts (<2%).

To highlight our method we set out to synthesize a member of the indazole natural product family— nigeplanine. Isolated from *nigella glandulifera*,^{2c} nigeplanine is one member of a small family of four indazole natural products, all of which contain the tricyclic pyridazino[1,2-*a*]indazolium ring system. Located largely in southwest and western China, the whole herb has been used as a folk remedy for a variety of ailments such as cold, cough, insomnia, and bronchial asthma. Nigeplanine and related nigellicine, have been synthesized previously by Kelly and co-workers.¹³ Their synthesis of nigeplanine proceeds by transformation of an isatin to give an advanced indazole intermediate, followed by alkylation of the indazole with 1,4,-dibromobutane, and subsequent decarboxylation and deprotection to give nigeplanine as the HBr salt (**1**) in 12 steps and 13 % overall yield.

Our synthesis began from commercially available 3-fluoro-5-methylphenol (**20**) (Scheme 3). The phenol was alkylated with cesium carbonate and methyl iodide in DMF to give **21**. We expected the methoxy and fluorine functions to direct ortho lithiation,¹⁴ which occurred at the desired position and led to formylation with DMF to afford **22** as a single regioisomer. We synthesised the aniline using pyrrolidine under S_NAr conditions (DSMO, potassium carbonate, 100 °C) to give **23** in good yield. The cyclization cascade of this compound went smoothly on the gram scale to yield methylated nigeplanine **24**. Deprotection of the methoxy group was carried out with Kelly's reported method, using BBr₃ in DCM to give 1.6 grams of the natural product nigeplanine as the HBr salt (**1**), in 5 steps and ~47 % overall yield. Pentane diffusion into a methanol/chloroform solution of **1** provided single crystals suitable for X-ray diffraction. The pale yellow bars crystallized as a non-merohedral twin¹⁵ and refinement confirmed the structure of **1**.

In summary we report the serendipitous discovery of a new precursor for the one step preparation of indazoles, and crystal structures of oxime **2** and the corresponding indazole **3** that provide clues to the reaction mechanism. The reaction conditions were generalized to afford several examples of the tricyclic pyridazino[1,2-*a*]indazolium ring system (**9-18**), and extended to the gram scale synthesis of nigeplanine hydrobromide **1**. We note in passing that many of these indazolium ions are fluorescent with colors of blue (**9**), blue/green (**1**), and purple (**15**). As this method quickly affords indazolium analogs of the natural product, their fluorescence may provide an opportunity for cellular imaging studies in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the Skaggs Institute and the NIGMS (GM 27953) for financial support. A.C.S. is a Skaggs Pre-doctoral Fellow and ARCS scholar. A Ruth L. Kirschstein Postdoctoral fellowship for O.B.B. was provided by NIH (F32GM087068). We would also like to thank Dr. Curtis E. Moore (UCSD) for assistance with solution of the X-ray structures.

References

- (1). Schmidt A, Beutler A, Snovydyovych B. Eur. J. Org. Chem. 2008:4073–4095.
- (2)(a). Atta-ur-Rahman MS, He CH, Clardy J. Tetrahedron Lett. 1985; 26:2759–2762.(b) Atta-ur-Rahman MS, Malik S, Hasan S, Choudhary MI, Ni C, Clardy J. Tetrahedron Lett. 1995; 36:1993–1996.(c) Liu Y, Yang J, Liu Q. Chem. Pharm. Bull. 2004; 52:454–455. [PubMed: 15056964] (d) Ali Z, Ferreira D, Carvalho P, Avery MA, Khan IA. J. Nat. Prod. 2008; 71:1111–1112. [PubMed: 18471018]
- (3)(a). Han W, Pelletier JC, Hodge CN. Bioorg. Med. Chem. Lett. 1998; 8:3615–3620. [PubMed: 9934481] (b) Patel M, Rodgers JD, McHugh RJ Jr. Johnson BL, Cordova BC, Klaba RM,

- Bachelor LT, Erickson-Viitanen S, Ko SS. *Bioorg. Med. Chem. Lett.* 1999; 9:3217–3220. [PubMed: 10576691] (c) Sun J-H, Teleha CA, Yan J-S, Rodgers JD, Nugiel DA. *J. Org. Chem.* 1997; 62:5627–5629.
- (4). Mosti L, Menozzi G, Fossa P, Filippelli W, Gessi S, Rinaldi B, Falcone G. *Arzneim.-Forsch./Drug Res.* 2000; 50:963–972. [PubMed: 11148862]
- (5)(a). Jakupec MA, Reisner E, Eichinger A, Pongratz M, Arion VB, Galanski M, Hartinger CG, Keppler BK. *J. Med. Chem.* 2005; 48:2831–2837. [PubMed: 15828821] (b) Showalter HDH, Angelo MM, Berman EM, Kanter GD, Ortwine DF, Ross-Kesten SG, Sercel AD, Turner WR, Werbel LM, Worth DF, Elslager EF, Leopald WR, Shillis JL. *J. Med. Chem.* 1988; 31:1527–1539. [PubMed: 3397990]
- (6). Goodman KB, Cui H, Dowdell SE, Gaitanopoulos DE, Ivy RL, Sehon CA, Stavenger RA, Wang GZ, Viet AQ, Xu W, Ye G, Semus SF, Evans C, Fries HE, Jolivet LJ, Kirkpatrick RB, Dul E, Khandekar SS, Yi T, Jung DK, Wright LL, Smith GK. *J. Med. Chem.* 2007; 50:6–9. [PubMed: 17201405]
- (7)(a). Schmidt A, Snovydyovych B, Habeck T, Drottboom P, Gjikaj M, Adam A. *Eur. J. Org. Chem.* 2007:4909–4916.(b) Schmidt A, Snovydyovych B, Gjikaj M. *Synthesis.* 2008; 17:2798–2804.
- (8). Jothibasu R, Huynh HV. *Chem. Commun.* 2010; 46:2986–2988.
- (9)(a). Wheeler RC, Baxter E, Campbell IB, Macdonald SJF. *Org. Process Res. Dev.* 2011; 15:565–569.(b) Spiteri C, Keeling S, Moses JE. *Org. Lett.* 2010; 12:3368–3371. [PubMed: 20608661] (c) Counciller CM, Eichman CC, Wray BC, Stambuli JP. *Org. Lett.* 2008; 10:1021–1023. [PubMed: 18229936] (d) Wray BC, Stambuli JP. *Org. Lett.* 2010; 12:4576–4579. [PubMed: 20849145] (e) Inamoto K, Katsuno M, Yoshino T, Arai Y, Hiroya K, Sakamoto T. *Tetrahedron.* 2007; 63:2695–2711.(f) Lukin K, Hsu MC, Fernando D, Leanna MR. *J. Org. Chem.* 2006; 71:8166–8172. [PubMed: 17025307] (g) Jin T, Yamamoto Y. *Angew. Chem., Int. Ed.* 2007; 46:3323–3325.(h) Stadlbauer W. *Sci. Synth.* 2002; 12:227–324.
- (10). Dale TJ, Sather AC, Rebek J Jr. *Tetrahedron Lett.* 2009; 50:6173–6175.
- (11). Hassner A, Michelson MJ. *J. Org. Chem.* 1962; 27:298–301.
- (12)(a). Ruiz JR, Arán VJ, Stud M. *Tetrahedron Lett.* 1988; 29:697–700.(b) Arán VJ, Asensio JL, Ruiz J, Stud M. *J. Chem. Perkin Trans. 1.* 1993:1119–1127.(c) Waldron NM, Montevalli M, Azam S, Dasopoulos PC. *J. Chem. Soc., Chem. Commun.* 1995:81–82.(d) Waldron NM, Raza M. *J. Chem. Soc., Perkin Trans. 1.* 1996:271–276.
- (13). Elliott EL, Bushell SM, Caverio M, Tolan B, Kelly TR. *Org. Lett.* 2005; 7:2449–2451. [PubMed: 15932220]
- (14). Marzi E, Mongin F, Spitaleri A, Schlosser M. *Eur. J. Org. Chem.* 2001:2911–2915.
- (15). TWINABS - Bruker AXS scaling for twinned crystals - Version 2012/1

Figure 1. Initial reaction discovery (top). Crystal structure of oxime 3 (bottom left). Crystal structure of indazole 4 (bottom right).

Scheme 1.

Proposed mechanism for the synthesis of fused indazolium ring systems.

Scheme 2.

Scope of the reaction with substituted 2-pyrrolidinyl benzaldehydes. Isolated yields are reported.

Scheme 3.

Gram scale synthesis and crystal structure of negeglanine hydrobromide (1). Counter anion is omitted for clarity.